R E M A R K S:

The purpose of this amendment is merely to supply a clarified version of the claims in the case. In this connection, it is noted that in the Office Action of September 17, 1982, reference was not made to the preliminary amendment which was submitted in this case with the filing papers.

It is hereby requested that that amendment which is superfluous not be entered.

Also, there is enclosed herewith a copy of each of (1) J. Cereb. Blood Flow Metabol., 2, No. 2, page 268, 1982; (2) Acta Neurologica Scandinavica, 65, Suppl. 90, pp77-78, 1982; (3) Acta Neurochirurgica, 63, 297-302 and 283-290, 1982; and CBF Bulletin 3/1982, pages 47-51. These references describe the advantageous effects (including clinical data) of Nimodipine, the compound used according to the present invention.

Respectfully submitted,

SPRUNG HORN KRAMER & WOODS

By _____
Joseph G. Kolodny
Reg No. 16,970

600 Third Avenue
New York, N.Y. 10016
(212) 661-0520

rCBF Bulletin 3, 47–51, 1982

DR. KAZDA

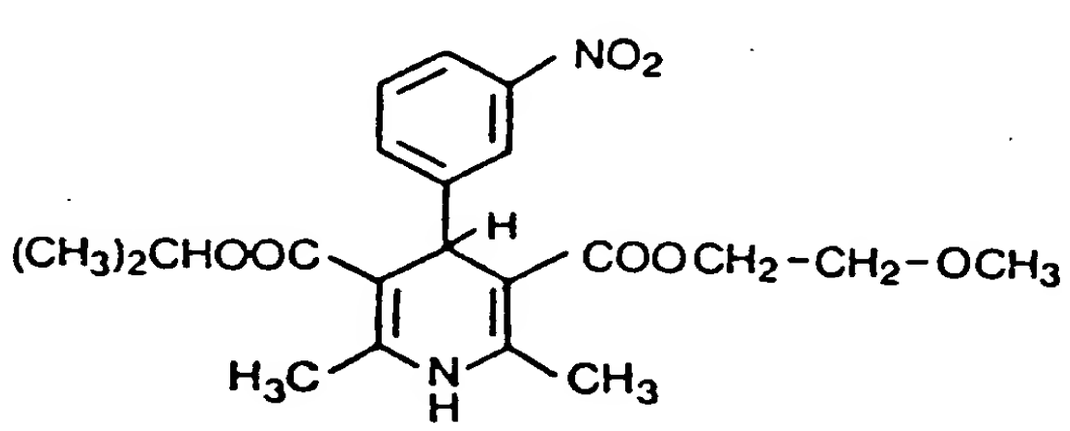
Calcium antagonism: A new therapeutic principle in stroke and cerebral vasospasm?

M. R. Gaab, A. Brawanski, J. Bockhorn, I. Haubitz, Ch. P. Rode and V. A. Maximilian
Neurosurgical Clinic, Institute of Nuclear Medicine and computer center, University of Würzburg, F.R.G.

In cardiovascular diseases, „calcium antagonism" using Verapamil or more recently Nifedipine plays an increasingly accepted role in therapy[5,6]. Experimental investigations have shown a Ca^{++} antagonistic vasoactivity also in the cerebral arteries[19,21,22] and the cerebral vascular smooth muscle seems to be still more sensitive to drugs blocking the Ca^{++} influx[21,22]. Especially a 1.4-dihydropyridine named Nimodipine, a derivative of Nifedipine (Fig. 1) developped by *Bayer AG*, revealed a predilective cerebrovascular action in animal experiments. Here, it could inhibit the vascular spasm following experimental SAH[1,18,20] as well as the postischemic impaired reperfusion and its sequelae in different models of cerebral ischemia[11,12,13]. These effects of Nimodipine are attributed to the inhibition of the spasmogenic calcium influx following potassium depolarization of the vascular smooth muscle[12,22]. This mechanism may also be of great importance in clinical cerebrovascular disease. The main purpose of this study was to assess the acute effects of Nimodipine on the cerebral blood flow (CBF) and related parameters.

Patients and Methods

The measurements were performed in 44 patients who had been admitted to the CBF laboratory for a clinical investigation of the regional cerebral blood flow (rCBF) pattern possibly altered by cerebrovascular pathology. In twelve patients (aged 26-64 y) with TIA, PRIND or minor arteriosclerotic stroke, a double rCBF study was performed within 60 minutes without any drug administration in order to investigate the reproducibility of the individual rCBF pattern (test-retest-procedure). The remaining 32 patients received 40, 60 or 80 mg of Nimodipine as an oral bolus dose immediately after the first rCBF investigation and, after 60 minutes, a second rCBF study was performed. This interval of one hour is suggested by pharmacological data which show a maximum plasma level of Nimodipine at this time. Twenty-five of these patients suffered from a TIA, PRIND or a minor arteriosclerotically based stroke following a history of hypertension and the investigation was performed in the acute phase (within less than three weeks following the attack). In seven patients, an acute SAH had been observed within 8 days before the study; in all patients, an increasing psychosyndrome and/or neurological deficits without focal intracranial bleeding suggested a cerebral vasospasm, which indeed has been proven in 5 of the 7 patients by a previously performed angiography[4]. The rCBF was measured with a standard 32 detector Cerebrograph (Novo Diagnostic Systems, Hadsund) using the Xe-inhalation technique (the Fourier analysis method[17]) on patients in supine position who had at least 15 minutes bedrest in a darkened and sound-attenuated laboratory. Using own programs[3,4] we were able to group the 32 detectors according to anatomical-topographic landmarks into six cortical areas of interest over each hemisphere. These regions were compared before and after therapy. Furthermore, in each patient separate detectors were chosen using a criterion of an at least 10% deviation above or below the individual mean hemispheric ISI level in order to control for possible interregional „steal" effects. We could thus monitor whether any fluctuations were evident in high-vs. low perfusion areas during drug therapy. The arterial blood pressure and the blood gases were measured during the first and second investigation and 30 minutes after drug administration. The statistical evaluation of the data was done with a TR 440 computer using own programs; ISI values were corrected to a standard-pCO_2 of 40 mm Hg (4% per mm Hg)[3,9].



BAY e 9736, Nimodipin

Fig. 1: Structural formula of „Nimodipin" (BAY e 9736, BAYER AG)

Results

Test-retest-procedure without drug therapy

In these 12 patients not only the mean hemispheric ISI was nearly identical during first and second

nvestigation, but also the regional value of the single detectors was highly reproducible. This can be clearly shown in Figure 2: There is no difference between the mean ISI and the values of the detectors with low perfusion (≦ 10% below mean flow) and the CBF over high perfusion areas (≧ 10% above mean CBF) remained stable as well. Blood pressure and arterial pCO_2 remained also stable during the second measurement (Fig. 2b). Our investigation technique gives consequently a good test-retest-correspondence within the interval of 1 hour and allows a reliable demonstration of acute drug effects.

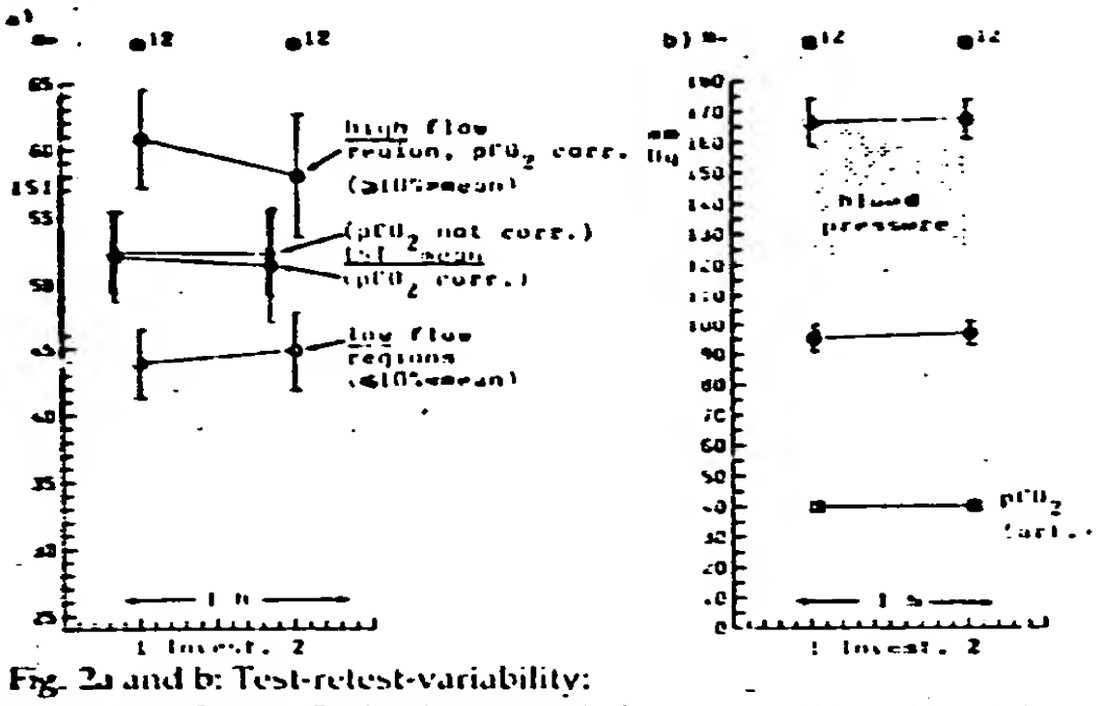


Fig. 2a and b: Test-retest-variability:
The mean ISI, the CBF in low (10% below mean ISI) and in high (10% above mean ISI) flow areas, the art. pCO_2 and the blood pressure were almost identical in the first and second investigation (no therapy, interval 1 hour; n = 12)

Overall effects of Nimodipine

Regarding only the mean hemispheric ISI (Fig. 3a) we found in the group of 32 patients a statistically significant flow increase (Wilcoxon's Rank Test) of about 8%. No difference was found between actual and pCO_2-corrected values; the arterial pCO_2-tension was not significantly altered by Nimodipine (Fig. 3b). The blood pressure, however, was markedly decreased, the fall in systolic pressure being more pronounced, and reaching its lowest value 30 minutes after administration of the drug (Fig. 3b). As the mean ISI increase is relatively small, a pathopsychological differentiation of the diagnoses was attempted.

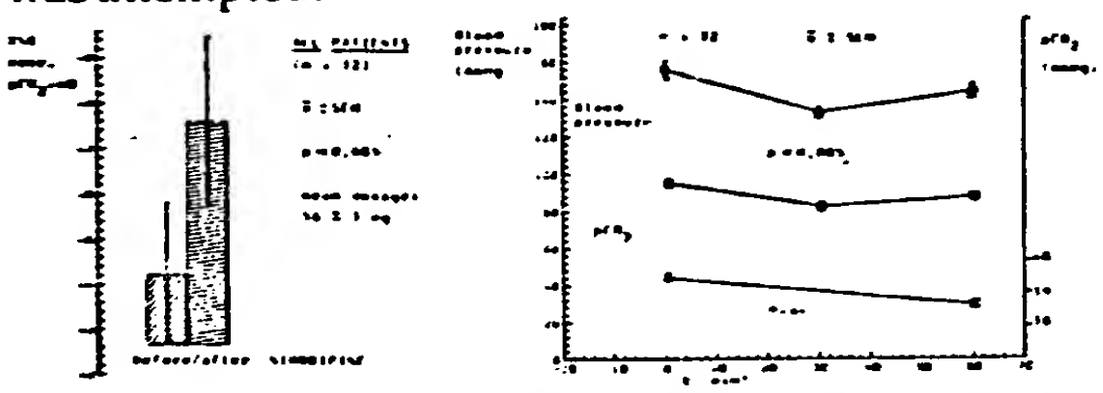


Fig. 3a and b: Overall effects of Nimodipine in patients with stroke and vasospasm. The mean ISI increases about 8%, the art. blood pressure shows a slight drop, predominantly of the systolic value, with a maximum at 30 min after Nimodipine administration; non-significant pCO_2 changes.

Nimodipine therapy in cerebral vasospasm

In the 7 patients with diffuse cerebral vasospasm following SAH, (which was also documented by angiography[4]), the reaction of Nimodipine was clearly better than in patients with arteriosclerotic stroke (Fig. 4a). In the spastic vessel, we achieved a mean CBF increase of about 14%, although the dosage of orally given Nimodipine was equal in both groups. The blood pressure-reaction was also different: In the patients with subarachnoid hemorrhage, the initial arterial pressure was only moderately elevated, and these values were not significantly altered by Nimodipine (Fig. 4b). The arterial pCO_2 also remained unchanged as in the no-therapy control group (Fig. 4b/Fig. 2b).

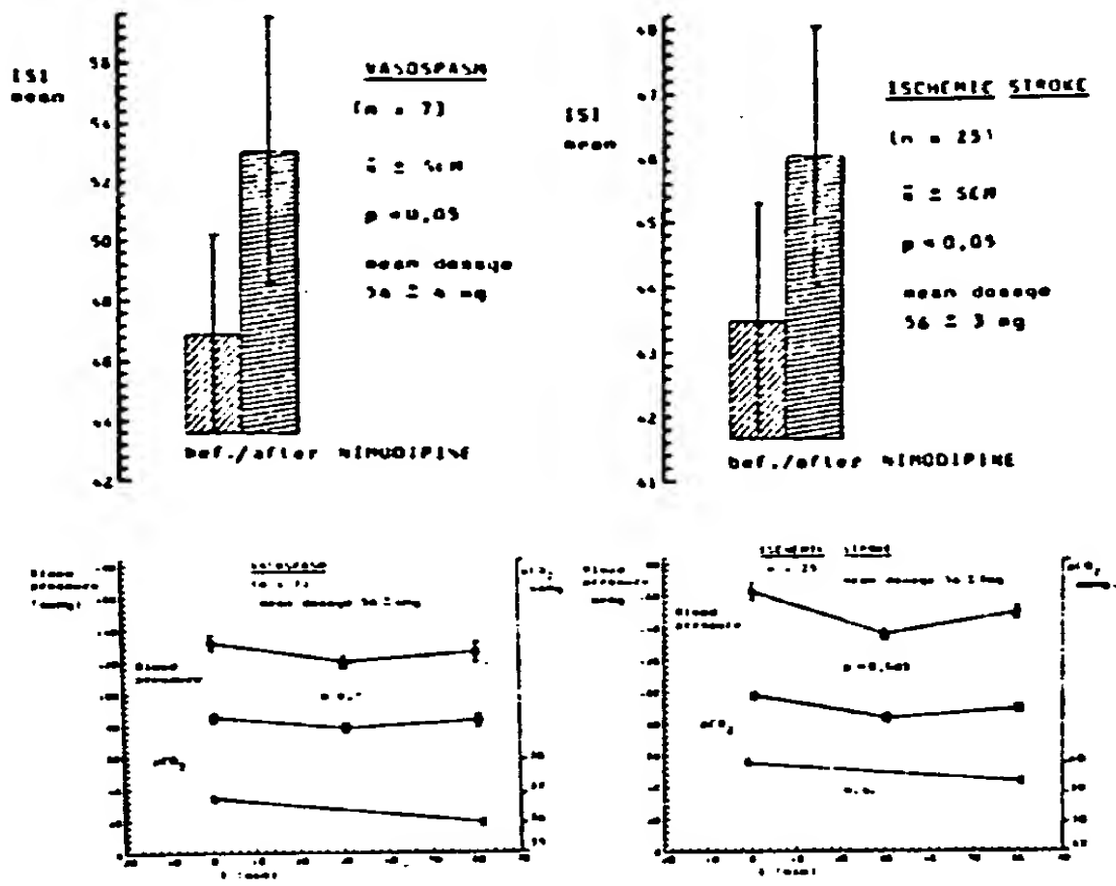


Fig. 4a and b: Different effect of Nimodipine in vasospasm following SAH and in ischemic stroke on hypertonic base: In vasospasm, the CBF increase is clearly higher (a); the blood pressure values are only significantly lowered in stroke patients, whose initial art. pressures are markedly higher.

Effect of Nimodipine in arteriosclerotic stroke

The group of 25 with ischemic stroke cases was strictly limited to patients suffering from idiopathic arterial hypertension which was considered as the main pathophysiological factor causing the TIA, PRIND or minor completed stroke in these individuals. In these relatively uniform stroke diseases, we found a significant mean hemispheric ISI increase of 6% ($p < .05$, Fig. 4a). In these patients too, the arterial pCO_2 was not significantly affected (Fig. 4b). However, the reaction of the blood pressure was different: The patients with stroke had a significantly higher initial arterial blood pressure than the patients with vasospasm according to the different pathophysiology (Fig. 4b), and this elevated blood pressure is markedly lowered by Nimodipine. It was a general finding that the higher

the arterial pressure, the bigger the fall. However, we have never seen a dangerous hypotension following oral administration of Nimodipine, the pressure always remaining above 115/70 mm Hg. The decrease in arterial pressure had its maximum 30 minutes after the drug's ingestion (Fig. 4b).

Comparing the different dosage given to our stroke patients (Fig. 5), the small differences between 40, 60 or 80 mg p. o. are not significant. It must be mentioned here that the initial CBF before therapy was by chance higher in the patients receiving a larger Nimodipine dosage.

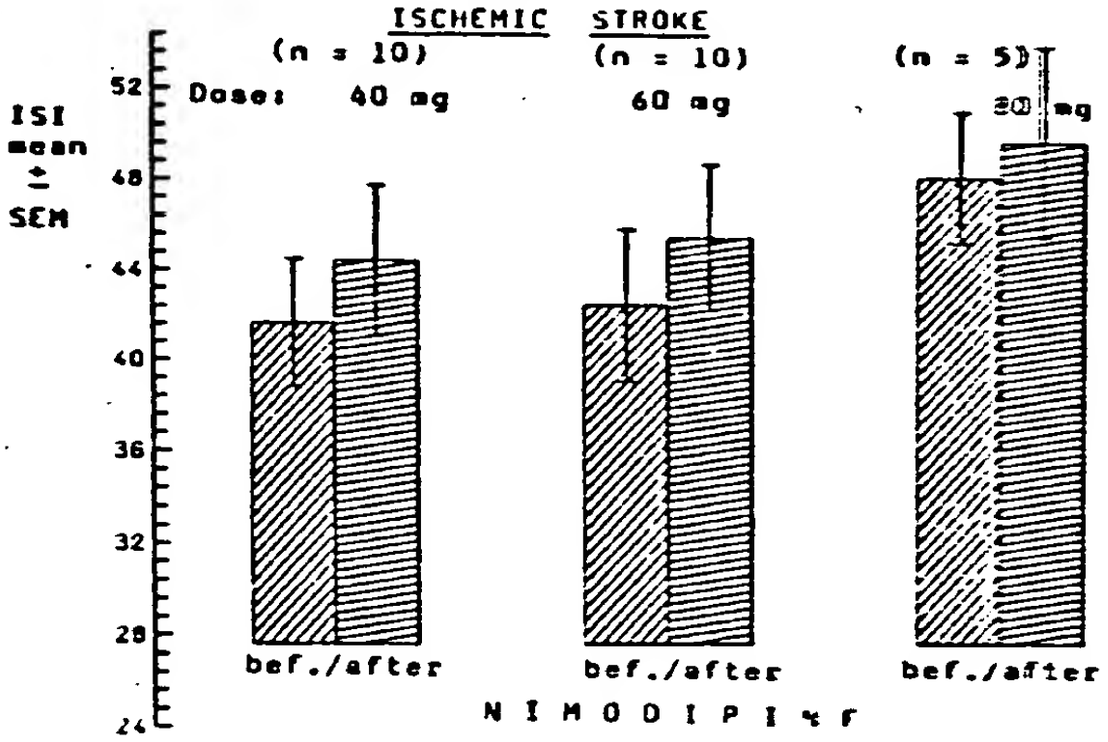
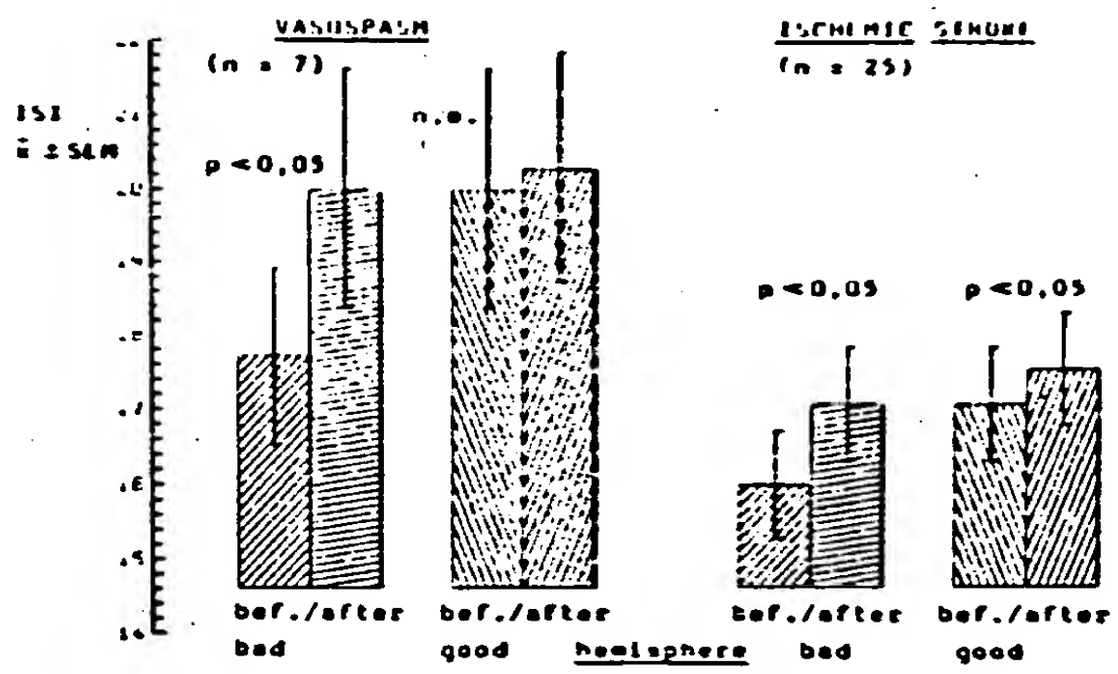


Fig. 5: Effect of different Nimodipine dosage in stroke patients. The effects of a single dose of 40, 60 or 80 mg Nimodipine given orally 1 h before 2nd investigation are not significantly different. Note the small number of patients in 80 mg-group with (by chance) higher initial mean ISI.

Differentiation of the effects on regional perfusion changes

When a drug increases the CBF, the question arises as to whether this effect is limited to regions with normal vascular reactivity, or is it possibly achieved at the expense of blood supply to already impaired areas. The occurrence of such an unfavorable steal effect would clearly speak against the clinical use of such a drug. If we compare however the reaction of the unequally perfused hemispheres (Fig. 6a), no indication for a „steal effect" can be seen. On the contrary, the less perfused hemisphere shows a higher increase of CBF than the better perfused side in stroke as well as in vasospasm.

Further evidence of the absence of a steal phenomenon is obtained by comparing the reaction of the cerebral regions, which have at least a ten percent lower perfusion than the corresponding mean hemispheric value, than those with a perfusion of ten percent or more above the mean hemispheric value (Fig. 6b). Here, the effect of Nimodipine in the low flow areas is again significantly better than



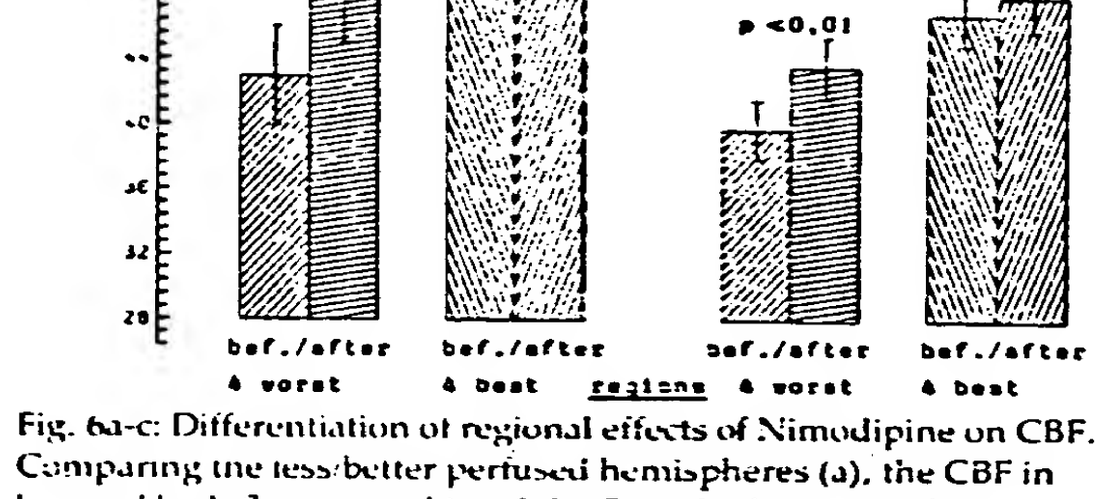


Fig. 6a-c: Differentiation of regional effects of Nimodipine on CBF. Comparing the less/better perfused hemispheres (a), the CBF in low and high flow areas (b) and the flows in the 4 worst/best regions of the patients (c), the ISI is always higher in the lower perfused areas. This predominant effect in reduced perfusion is more pronounced in stroke whereas in vasospasm the ISI increase is more generalized, with the exception of the hemispherical difference (a).

in the high flow regions and this difference was more pronounced in the stroke patients. The same holds true when the four worst perfused regions of the cerebral hemispheres are compared with the four best perfused areas (Fig. 6c).

The best evidence for the absence of an adverse „steal effect" is given by a ranked evaluation (Fig. 7). Here, the regions are ordered in sequence from worst to best perfusion during first rCBF investiga-

ion. The reaction of these ranked regions to Nimodipine therapy is then calculated and plotted, and the mean increase of CBF in these regions can be seen as the difference between the two lines. The increase in flow following Nimodipine is markedly higher in the worst perfused areas; here, the improvement may exceed 20%, whereas regions which initially were always well perfused do not further react. The preference of Nimodipine activity for low perfused areas can only be demonstrated in stroke patients; in vasospasm, there is an overall and relatively uniform rise of CBF in all regions (Fig. 7b).

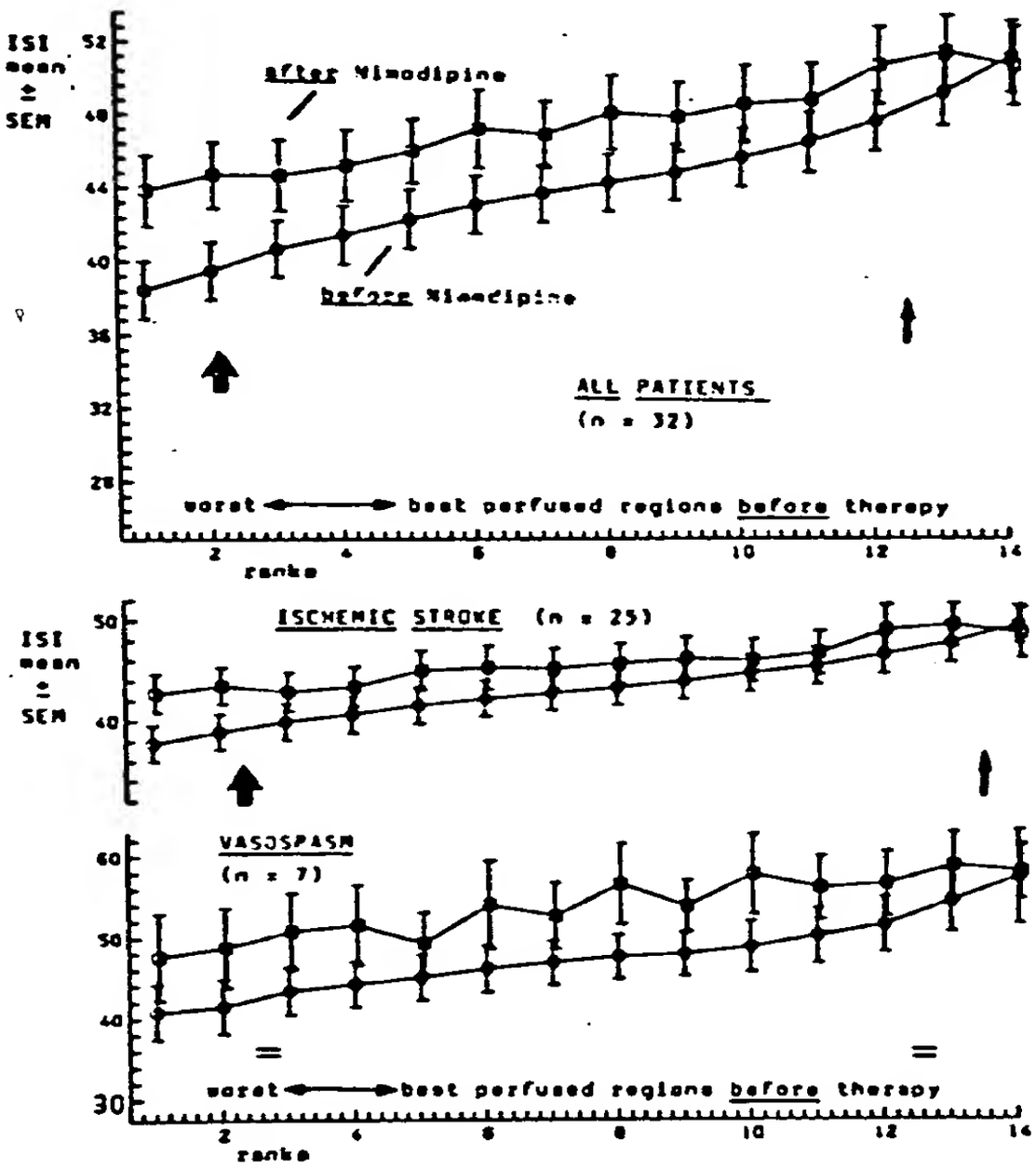


Fig. 7a and b: Ranked evaluation of Nimodipine effects on regional perfusion differences: When ordered from worst to best regions, the less perfused areas show a higher increase in CBF following Nimodipine (a). This predominance is more pronounced in stroke patients, whereas in vasospasm, a more generalized CBF increase is seen (b).

Discussion

Nimodipine is a vasoactive substance, whose vasodilatatory effect is attributed to a selective inhibition of the Ca^{++}-influx into the K^{+} depolarized vascular smooth muscle[12,13,22]. This inhibition of Ca^{++}-influx uncouples the mechanical reaction of the smooth muscle from the electrical depolarization without interference with adrenergic or cholinergic membrane receptors.

This principle of „calcium antagonism" is now increasingly used in cardiovascular diseases therapy[5,6]. Here, the calcium antagonists Nifedipine, from which Nimodipine is derived, and the somewhat different Verapamil are in concurrence with β-blocking agents as „therapy of first choice" in coronary-artery insuffiency[5,6,10]. Especially remarkable is the immediate activity of Nifedipine in coronary spasm[5,10]. Compared to Nifedipine, Nimodipine more selectively dilates the cerebral vessels. In isolated arteries, experimental contractions of the basilar artery caused by serotonin, phenyleferin and other agonists were very effectively inhibited by Nimodipine, whereas this action was missed in the A. saphena[21,22]. Using intraarterial or intravenous infusion, the CBF in dog, monkey, cat and rat was very effectively increased (up to more than 70%[21,22]), whereas only a slight increase in heart rate, and a small decrease in arterial pressure was recorded. The pCO_2 did not change. This led to our investigation of Nimodipine effects in clinical cerebrovascular diseases. Nimodipine reportedly did not show adverse side effects in long-time oral administration and it was only given orally in this first investigation. Our group did not observe any negative effects in the present 32 patients following Nimodipine ingestion either.

Our results show a significant overall increase in the CBF following Nimodipine but this effect with 8% flow augmentation is relatively small. Kohlmeyer requests a mean CBF increase of at least 7% under the condition of a stable pCO_2[14] for a clinical significance of CBF changes within a short interval. On the other hand, most investigations with repeated rCBF measurements using the Xe-clearance method showed a tendency of lower values during the second study[8,15,16]. Besides technical reasons, this obtained lower value during the second measurement is attributed to the lower anxiety and stress of the patient. As our „control values" in patients with a test-retest-procedure (no-therapy) are almost identical with even smaller variations than mostly reported in the literature, we attribute the changes in global and regional CBF to a true effect of Nimodipine.

In arteriosclerotically based stroke, this small but significant improvement in CBF confirms the results of the animal experiments mentioned above. The minor increase found in our patients may be explained by the oral administration of the drug which is only partially absorbed and by the rigidity of the arteriosclerotic vessel. With most other vasodilators, an effect on the arteriosclerotic cerebral vessel was missed[8,9], or an increase in CBF was restricted to normal areas often at the expense of the regions with already reduced perfusion. The absence of such an unfavorable steal effect and even the predominance of Nimodipine activity in low-flow

reas was the most exciting finding of our study. This favorable effect in the disturbed regions may be attributed to an antispastic effect and an additional vasospasm in the injured brain tissue in stroke as well as in head trauma is under discussion[2,7]. In the damaged brain tissue the vascular smooth muscle should be K^+-depolarized to some degree due to the hypoxia, as the maintenance of the polarisation of the vascular muscle is energy consuming. The Nimodipine antagonism to the calcium influx into the depolarized muscle could then explain the predominant CBF increase in the tissue with impaired perfusion. This is not only in accordance with animal experiments[19,20,21,22], but was also confirmed by our results in the second group of patients.

In vasospasm, the effect of Nimodipine is much better than in patients with arteriosclerotic cerebrovascular disease. This did not surprise us, as the spastic vessel without irreversible anatomical changes can certainly dilate much more than the vascular wall with sclerotic transformations. The advantage of Nimodipine is the independence of its action from the pathophysiology of the spasm, as it directly impedes the electro-mechanical coupling in the smooth muscle. However, this mere calcium antagonism suggests the possibility of a „rebound effect": as the depolarization of the cell is not prevented, a fall in Nimodipine concentration may immediately lead to a calcium influx with spastic contraction.

The present results certainly stimulate further investigations on Nimodipine in cerebrovascular diseases. Besides the long-time effects of Nimodipine on CBF and other technical values given by different application modes, the reaction of the clinical symptoms and the clinical course of the disease should be investigated. Here, the often rapid improvement of neurological deficiencies in our patients with vasospasm is an encouraging sign.

Summary

Using Xe inhalation technique, the effect of the new calcium antagonist Nimodipine (*Bayer*) on regional and global CBF in 32 patients with cerebrovascular diseases was investgated. Following single oral application of 40 to 80 mg Nimodipine, the CBF retested after one hour showed a global increase of about 8%. As we found almost identical flow values in a preceding test-retest-evaluation of our Xe method in 12 patients with no therapy, this small but significant increase is attributed to a true cerebrovascular activity of Nimodipine. In stroke on arteriosclerotic base (25 patients), a mean CBF increase of about 6% is seen after administration of Nimodipine and the regional analysis showed no steal effect. On the contrary, Nimodipine especially improves the rCBF in the low flow areas. Here, the rCBF increase reaches 20% in a ranked evaluation. The blood pressure is thereby moderately lowered, the arterial pCO_2 remains unchanged. In cerebral vasospasm following SAH (7 patients), Nimodipine more markedly increased the CBF (about 14% hemispheric mean increase). According to the diffuse vascular spasm, the regional analysis reveals a more generalized rise in rCBF compared to sclerotic stroke. These positive effects of Nimodipine on CBF in stroke and vasospasm without any indication of an adverse intracerebral steal effect suggest further investigations on its clinical usefulness.

Acknowledgements

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ACTA
NEUROCHIRURGICA

Department of Neurosurgery, Academic Hospital, Groningen, The Netherlands

Effect of Nimodipine (Bay e 9736) on Postischaemic Cerebrovascular Reactivity, as Revealed by Measuring Regional Cerebral Blood Flow (rCBF)

By

H. J. Gelmers

Summary

Regional cerebral blood flow (rCBF) was measured, using the xenon-133 intracarotid injection technique in 10 patients with an acute ischaemic stroke, involving the cerebral cortex, before and after intravenous injection of a single dose of nimodipine (Bay e 9736). After nimodipine application in all patients a dose dependent increase of hemispheric blood flow was observed. In the regional pattern the stroke area showed, after nimodipine in 9 patients relatively similar changes in blood flow as the hemispheric flow did. In three of these patients the increase reached such a level, that the presence was concluded of an inverse steal phenomenon. The intracerebral steal phenomenon was not observed. As a side effect in one patient a mild fall in blood pressure and sinusbradycardia was observed, of short duration.

Introduction

The neurological status of a patient having a subarachnoid hemorrhage influences both the mortality rate and the manner of survival (Botterell *et al.* 1958, Hunt and Hess 1968). Amongst the complicating factors influencing the neurological status, vasospasm is of major importance, resulting in ischaemic damage of the brain. There are no differences in ischaemic changes after stroke (Paulson 1971) or subarachnoid haemorrhage (Gelmers 1979) as assessed by measurements of regional cerebral blood flow (rCBF). In this study we report the influences of a new pharmacological agent (nimodipine, Bay e 9736) on the postischaemic cerebrovascular reactivity in patients with an acute ischaemic stroke, measuring rCBF.

Patients

From a group of consecutive patients referred for acute ischaemic stroke, ten were selected, who underwent for various reasons, cerebral angiography, which in our department is electively undertaken. All patients underwent a complete neurological work-up, including spinal fluid tap, electroencephalography, skull X-rays and CT-scans. Patients with severe hypertension were excluded from the study. No other medication was given other than digitalis preparations, antibiotics or diuretics.

Six of the patients were male and four were female. Their mean age was 64.4 ± 6.3 years. In eight patients the stroke was due to a thrombosis; in two to an embolism, most probably of cardiac origin. As the CT scan depicted, in all patients the stroke involved the cortical structures. Informed consent was obtained from all patients, following a full explanation of the measurement procedures.

Methods

rCBF was measured, using the *xenon-133 intracarotid injection technique*. Basic features of the method and the 254-channel equipment have been extensively described elsewhere (Olesen *et al.* 1971, Sveinsdottir *et al.* 1977, Gelmers 1978).

The patients were studied in addition to cerebral angiography, without using premedication. After the administration of local anaesthesia at the site of the puncture (femoral artery in the groin), the internal carotid artery was cannulated with a thin heparinized polyethylene catheter (Seldinger technique). A 5 mCi bolus of xenon-133 dissolved in about 5 ml saline solution, was injected and the washout was followed with 254 collimated detectors, covering the affected hemisphere. Blood flow was computed as initial rCBF from the slopes of the semilogarithmically displayed clearance curves at 15 to 60 seconds after the peak.

In each patient three rCBF measurements were carried out within the same session. During the first measurement the patient was supine, in a physically and mentally relaxed state, with closed and covered eyes. The examination room was kept as silent as possible and the patients were not spoken to, or touched intentionally. None of them were observed to move or talk during the clearance period. This procedure was called "rest". Following this study, additional rCBF measurements were taken:

a) Testing reactivity to arterial pCO_2 changes.

The influence of changes in arterial pCO_2 was studied by breathing for one minute prior to and during the CBF measurement 10% CO_2. CO_2-reactivity was calculated as lnCBF/arterial pCO_2.

b) Testing the influence of nimodipine.

Nimodipine was given intravenously, in 5 patients in a dose of 15 µg/kg bodyweight, and in 5 patients in a dose of 30 µg/kg bodyweight. The mode of application was a bolus injection lasting up to 10 minutes. At the end of the bolus injection, the rCBF measurement was started.

Before each rCBF measurement, an arterial blood sample from the catheter was taken for blood gas analysis. Arterial pCO_2 of the rest measurement was taken as a reference value, correcting the subsequent rCBF values by 4% per mm Hg difference in arterial pCO_2 (Olesen *et al.* 1971, Gelmers 1978).

Blood pressure (mean arterial blood pressure, MABP) was measured intra-arterially with a pressure transducer and a blood pressure module (Philips, XV

1505). The time interval between consecutive tests was about fifteen minutes, long enough to be sure that practically all of the isotope used in the previous study has been washed out of the brain.

Reproducibility and Calculations

With the same methods and equipment rCBF was previously studied in the resting state in 18 neurologically normal patients. Mean hemispheric rCBF was 57.9 ± 13.0 ml/min per 100 g. Repeated resting state measurements revealed an interchannel coefficient of variation of $7.2\% \pm 3.8\%$ (mean $\pm$ S.D.) (Gelmers 1979).

In the clinical situation there is a considerable lack of homogeneity of the patient material, this reflecting mean rCBF values with a high degree of variability. Therefore, the comparison of mean CBF values before and after nimodipine application was rejected for statistical evaluation. Evaluation was performed by comparison of mean changes in CBF before and after nimodipine application with spontaneously occurring changes in repeated CBF measurements in neurologically normal patients. Although focal areas can easily be detected by visual comparison of the rCBF pattern, in this study a focus is defined as an area, represented by more than one neighbouring detectors, which are related to abnormalities at clinical examination and at CT.

Referring to reproducibility, thus an interchannel coefficient of variation, exceeding the mean $\pm$ 2 S.D. = 14.8% could be considered a significant change with a fairly high degree of certainty ($p < 0{,}05$). Focal flow alterations were compared to this error of measurement, using the t-test.

Results

When compared with the resting state, no systematic changes in mean arterial blood pressure or pulse rate were observed after application of nimodipine (except for one patient, who developed a tension drop and bradycardia, see later), and neither was there a systematic alteration in arterial pCO_2.

The responses to arterial pCO_2 changes in ten stroke patients were mildly impaired in comparison with the reference group of 18 neurologically normal patients (pCO_2-reactivity of the stroke group 0.036 ± 0.005 (mean $\pm$ S.D.), versus 0.040 ± 0.016 in the reference group, $p < 0.05$).

In all patients an intravenous dose of nimodipine resulted in an increase of hemispheric blood flow. The mean of increases after a dose of 15 µg/kg bodyweight were 3.0 ± 1.2 ml/min per 100 g ($p < 0.01$ as compared with a repeat measurement in a reference group) and after a dose of 30 µg/kg bodyweight 7.6 ± 3.2 ml/min per 100 g ($p < 0.0025$) (see Table 1).

In the regional flow pattern the stroke area was depicted as an area of focal hyperemia ($N = 4$) (see Table 2). In nine patients a relatively similar change in focal blood flow and hemispheric blood flow was

Table 1. *Effect of a Single, i.v. Dose of Nimodipine (Bay e 9736) on Hemispheric Blood Flow in Patients with Acute Ischaemic Stroke*

Stroke patient	Rest CBF	Rest pCO_2	Hypercapnia CBF	Hypercapnia pCO_2	pCO_2-reactivity	Test CBF	Test pCO_2	ΔCBF*
Nimodipine dose 15 µg/Kg/Bw.								
1	42	35	83	52	0.040	45	36	2
2	61	42	79	48	0.043	63	41	5
3	49	38	68	46	0.031	54	39	3
4	63	43	70	46.5	0.030	61	41	3
5	31	39	36	43	0.037	32	38	2
Mean	49.2							3.0
S.D.	13.3							1.2
Nimodipine dose 30 µg/Kg/Bw.								
6	52	34	76	43	0.042	70	36	13
7	54	39	65	45	0.031	61	39	7
8	42	37	66	47	0.041	51	38	7
9	30	39	38	46	0.034	35	38	7
10	39	34	68	50	0.035	51	38	4
Mean	43.4				0.036	55.1		7.6
S.D.	9.8				0.005	10.8		3.3

CBF expressed in ml·min.$^{-1}$ per 100 g; pCO_2 expressed in mm Hg; CO_2-reactivity calculated as $\Delta \ln CBF / \Delta pCO_2$; * ΔCBF (test-rest) calculated after CBF-test corrected for pCO_2.

observed. In three of those patients the focal flow increase was higher than the increase in hemispheric blood flow ($p < 0.01$ and $p < 0.001$). This type of flow change is known as the inverse cerebral steal phenomenon. In one patient a decrease in focal flow as compared to the hemispheric was observed, but the difference did not reach statistical significance. Therefore a cerebral steal phenomenon could not be concluded.

Side Effects

In one patient mild side effects were observed. For this reason the history is mentioned here more explicitly.

A 66-year old man, without any history of cardiac complaints, developed a right-sided paresis of the face, arm and leg, together with right-sided hemianopsia. There was no aphasia. Four months earlier he had a T.I.A. of his right arm of 10 minutes duration. There was a rough

Table 2. *Effect of a Single, i.v. Dose of Nimodipine (Bay e 9736) on Regional CBF in Patients with Acute Ischaemic Stroke*

Stroke patient	Region	N*	**increase (+) or decrease (—)	p (t-test) test vs rest
1	lower frontal	28	+1.8 ± 3.8	n.s.
2	temporocentral	14	+13.0 ± 5.4	n.s.
3	lower frontal	36	+2.6 ± 4.2	n.s.
4	frontal	32	+17.9 ± 4.6	$p < 0.1$
5	upper frontal	24	+18.0 ± 2.7	$p < 0.01$
6	frontal	26	+8.2 ± 3.6	n.s.
7	parietal	18	—2.6 ± 3.2	n.s.
8	central	26	+73.4 ± 6.8	$p < 0.001$
9	central	22	+4.7 ± 3.5	n.s.
10	mid frontocentral	32	+48.5 ± 4.5	$p < 0.001$

* N = number of channels from which the mean increase or decrease is computed.

** The increase or decrease mean was calculated as follows:

$$\frac{1}{N} \sum^{i=N} \left[\frac{\text{test i} - \text{rest i}}{\text{rest i}} \right]$$

murmur over the left cervical region and on the third day after onset of neurological symptoms, angiography was undertaken. The left carotid artery showed a plaeque at the bifurcation, and intracranially the M_3 was missing. In addition, CBF measurements were performed. 5 minutes after intravenous injection of nimodipine (30 µg/kg bodyweight the patient had complaints of headache and he was yawning).

A tensiondrop was observed (bloodpressure 140/80 → 90/60), together with bradycardia (48/min., regular, equal). Within $2^1/_2$ minutes the tension was normal with a pulse rate of 92/min. A CBF measurement started in the meantime proved normal, and gave no unexpected findings. Electrocardiography half an hour after nimodipine application also proved normal.

Conclusion

After application of 30 ug/kg bodyweight nimodipine, a patient with an acute ischaemic stroke (3 days old), without any cardiac history, developed a tension drop and sinusbradycardia of short duration.

Discussion

For testing the effectiveness of drugs on cerebral haemodynamics, measurement of rCBF has proved to be a reliable method (McHenry

et al. 1970, Sh[illegible] and Paulson 1979 Olesen and Paulson 1971, Heiss 1973). It is difficult to obtain reliable criteria for determining a significant difference in rCBF between control and test values. This difficulty is due to spontaneous changes that occur with repeated measurement and to the methodological error of the measuring technique.

Since there is a considerable lack of homogeneity in the patient material with respect to severity and course of flow disturbances, CBF values during the resting state show a high degree of variability. To achieve statistical significance in tests based on comparison of mean values, drug-induced alterations of CBF would have to be very high. Therefore, the changes in flow with respect to the resting state have to be considered in the evaluation of drugs. The results in this study showed an dose-dependent improvement of mean hemispheric blood flow after intravenous application of nimodipine. From the drug-induced alterations in focal blood flow, compared with the drug-induced alterations in hemispheric blood-flow, the type of response to the pharmacological agent can be estimated. Fieschi *et al.* (1969) reported three types of rCBF response, namely homogenous, heterogeneous or no response. A homogeneous response is a relatively similar difference in all rCBF values between rest and test measurements in a given patient. Two different types of heterogeneous reaction may be observed (Paulson 1971): The intracerebral steal phenomenon, with an increase of flow through non-focal areas, shunting off blood from ischaemic non-reactive regions, and the inverse cerebral steal phenomenon, with an improvement of flow in ischaemic foci at the expense of well-perfused brain areas. In this study the intracerebral steal phenomenon was not observed, whilst in three patients the inverse cerebral steal phenomenon occurred.

Nimodipine is a musculotropic active compound of the new group of 1.4-dihydropyridine derivatives, the activity of which is based on its ability to block the influx of extracellular calcium to the smooth muscle cells. There is a preferential action on the cerebral vessels; it has been demonstrated that in vitro, the contraction of the basilar arteries of dogs and rabbits, induced by several different stimuli, can be inhibited only to a lesser degree (Towart and Kazda 1979). From these pharmacological data, influences on cerebral haemodynamics can be expected. Referring to the pharmacological properties of nimodipine, the conclusion must be that this substance counteracts the vascular mechanisms resulting in global ischaemia, probably by preventing contractile activity. Since nimodipine is a calcium antagonist and is related to nifedipine, inhibitory effects both on cardiac conduction, as well as on the contractile system of the smooth muscle of the arterioles can be expected (Deathen *et al.* 1980), resulting in a bradycardia and a tension drop.

rCBF studies in patients with subarachnoid haemorrhage depict global reduction as well as regions with focal ischaemia (Symon *et al.* 1972, Heilbrun *et al.* 1972, Gelmers *et al.* 1979). In cerebral ischaemia, as the result of middle cerebral artery occlusion, is shown that cerebral infarction and microvascular changes in cerebral ischaemia are associated with decreases of CBF in the infarcted area, and may occur in other regions of the affected hemisphere, whilst both are histopathologically related to slightly impaired as well as unimpaired brain tissue (Yamaguchi *et al.* 1971). There is no reason to believe that the pathophysiology of brain ischaemia and related events, such as postischaemic vascular reactivity in subarachnoid haemorrhage, although the result of various factors is basically different from that in stroke.

Since nimodipine in stroke patients has a beneficial effect on postischaemic cerebrovascular reactivity, as shown in this study, we therefore believe nimodipine may be of therapeutic value in the management of subarachnoid haemorrhage.

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Author's address: H. J. Gelmers, M.D., Ph.D., Department of Neurosurgery, Academic Hospital 59, Oostersingel, Groningen, The Netherlands.

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ACTA NEUROCHIRURGICA

Department of Neurosurgery, Kitasato University School of Medicine, Kitasato 1-15-1, Sagamihara, Kanagawa, Japan

Effect of Hyperdynamic Therapy on Cerebral Ischaemia Caused by Vasospasm Associated with Subarachnoid Haemorrhage

By

T. Tanabe, T. Saitoh, S. Tachibana, H. Takagi, and K. Yada

With 4 Figures

Summary

Ten patients who developed neurological deficits associated with angiographically proven cerebral vasospasm caused by ruptured aneurysm were treated with hyperdynamic therapy induced by administration of a large amount of human serum albumin. No vaso-active drugs were administered. Cardiopulmonary function and intracranial pressure were monitored during the treatment. Marked improvement of neurological function was observed in all cases. Nine patients recovered completely without any neurological residual following treatment. The degree of the improvement observed during treatment closely correlated with the decrease in total peripheral resistance. Infusion of albumin did not cause elevation of intracranial pressure. It was concluded that the hyperdynamic therapy induced by administration of albumin has a dramatic effect on the ischaemic cerebral insult caused by vasospasm. It is postulated that the main effect of this treatment is produced by cerebrovascular dilatation.

Introduction

Neurological deficits that develop in patients with vasospasm due to subarachnoid haemorrhage most likely result from ischaemia secondary to decreased cerebral blood flow[4,6]. Previous reported effective treatments of this condition are drug-induced arterial hypertension[4] and hypervolaemia in conjunction with hypertension[3]. However, drug induced hypertension and aggressive volume expansion may easily cause cardiopulmonary compromise[2,3]. To overcome this undesirable complication, we have recently treated patients with symptomatic

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Authors' address: T. Tanabe, M.D., T. Saitoh, M.D., S. Tachibana, M.D., H. Takagi, M.D., and Prof. Dr. K. Yada, Department of Neurosurgery, Kitasato University School of Medicine, Kitasato 1-15-1, Sagamihara, Kanagawa 228, Japan.

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Department of Neurosurgery, Graz University, Austria, and Division of Surgical Neurology, Research Institute of Brain and Blood Vessels, Akita, Japan

Prevention of Symptomatic Vasospasm by Topically Applied Nimodipine

By

L. M. Auer, Z. Ito, A. Suzuki, and H. Ohta

With 1 Figure

Summary

A 2.4×10^{-5} M solution of the Calcium-antagonist Nimodipine was administered to the exposed cerebral vessels in 17 patients intraoperatively clipping of a ruptured aneurysm. The interval between subarachnoid haemorrhage and operation was 48 to 72 hours. The CT investigation had revealed blood accumulation in the basal cisterns in all cases. Vasodilatation was observed in all instances; the percentage being greater in small vessels as compared to large vessels. Postoperatively, a neurological deficit combined with angiographically verified vasospasm occurred in two patients, but was reversible in both. Fifteen patients remained free from symptomatic vasospasm and were discharged without neurological deficit. In 13 of these patients and 3 additional cases, a plastic cannula was placed intraoperatively so that postoperative topical administration of Nimodipine was possible. Postoperative control-angiograms after a mean interval of 7 days from SAH did not show severe spasm in any of the patients; localised moderate asymptomatic spasm was found in 8 cases and was reserved in 5. Moderate postoperative symptomatic spasm was observed in 2 patients, treated and reversed in one patient. In 5 of 7 cases without evidence of spasm in the angiogram postoperative topical administration of Nimodipine caused vasodilatation. It is concluded, that topical intracisternal administration of Nimodipine reverses intraoperative vascular spasm and decreases the probability of postoperative symptomatic vasospasm after early surgery.

Introduction

Nimodipine*, a lipophilic Calcium-antagonist known to act via the receptor operated Calcium-channels[15] has predominantly shown cere-

* Bayer AG, Wuppertal.

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brovascular dilatation in experiments in cats[1]: Following intravenous administration, cerebral blood flow increased[5], and pial vessels dilated without a significant decrease in blood pressure[1]. In human volunteers and patients no complications have been observed after oral or intravenous therapy[9,10,12]. It seemed to be appropriate to try to prevent severe symptomatic cerebral vasospasm after subarachnoid haemorrhage (SAH) using this preparation because vasospasm is still considered to be one of the most severe complications in the clinical course of aneurysm patients apart from rebleeding from the ruptured aneurysm. Even after surgical treatment of the aneurysm in the acute stage and evacuation of the subarachnoid clot, severe symptomatic vasospasm occurs in 20-40% of patients reported in literature[2,4,6–8,11,13,14,16]. The following pilot series in patients has been designed in order to demonstrate the dilatory effects of Nimodipine intraoperatively as well as postoperatively.

Methods and Selection of Patients

In 20 patients, 32-65 years of age, 9 women and 11 men, SAH from a ruptured cerebral aneurysm was diagnosed by CT and angiography. Neurologically, the grading in accordance with the scale of Hunt and Hess[3] was "I" in one patient, "II" in 15 patients, "III" in 3, and "IV" in 1 patient. In the results of the CT scans, blood clots in the basal cisterns were found in all cases, minor in 3, moderate in 14 and severe in 3 patients. 6 patients had an aneurysm of the internal carotid artery (ICA), 6 of the middle cerebral actery (MCA), 7 of the anterior communicating artory (ACOM) and 1 of the anterior cerebral artery (A_2). Three patients had several additional unruptured aneurysms.

Surgery was performed on day 1-5 (mean day 2.5 after the last SAH, day of SAH = day 0). After unequivocal clipping of all aneurysms, (patients with partial or total wrapping being excluded from this study), subarachnoid clots were evacuated by irrigation and careful suction, but without special attention given to absolute removal of subarachnoid blood[7]. Thereafter, in 17 cases, the exposed vessels were bathed in a 2.4×10^{-5} M solution of Nimodipine for 10 minutes. Microphotographs were taken before and at 1 minute-intervals during the procedure. Special care was taken to protect the light-sensitive drug by wrapping the syringe filled with Nimodipine and by switching off the microscope-light except for the short periods during exposures. Before each photograph, some of the solution was sucked away to expose the vessels for photography; immediately afterwards a fresh solution was introduced, so that a total quantity of 20 ml of the Nimodipine solution was used. At the end of this procedure a plastic cannula was placed intracisternally near the aneurysm clip in 13 patients treated with Nimodipine intraoperatively and 3 additional patients and left there for 3-10 days. On day 5-12 after SAH (mean 6.5 days), a control angiogram was performed in all patients. Thereafter, 200 µg Nimodipine was administered topically through the plastic cannula into the basal cisterns by continuous infusion over 10 minutes. Further control angiograms were performed at the end of the 10 minute infusion period and 10 minutes thereafter to demonstrate reversal of spasm and/or dilatation of vessels with normal calibre.

Results

Dilatation was found in all observed vessels treated intraoperatively, *i.e.*, the internal carotid artery, the anterior cerebral artery, the middle cerebral artery and their major branches, as well as smaller branches like Heubner's artery, the anterior chorioidal artery and posterior communicating artery. The percentage dilatation ranged between 13 and 140%; small vessels dilating more than large ones (Fig. 1).

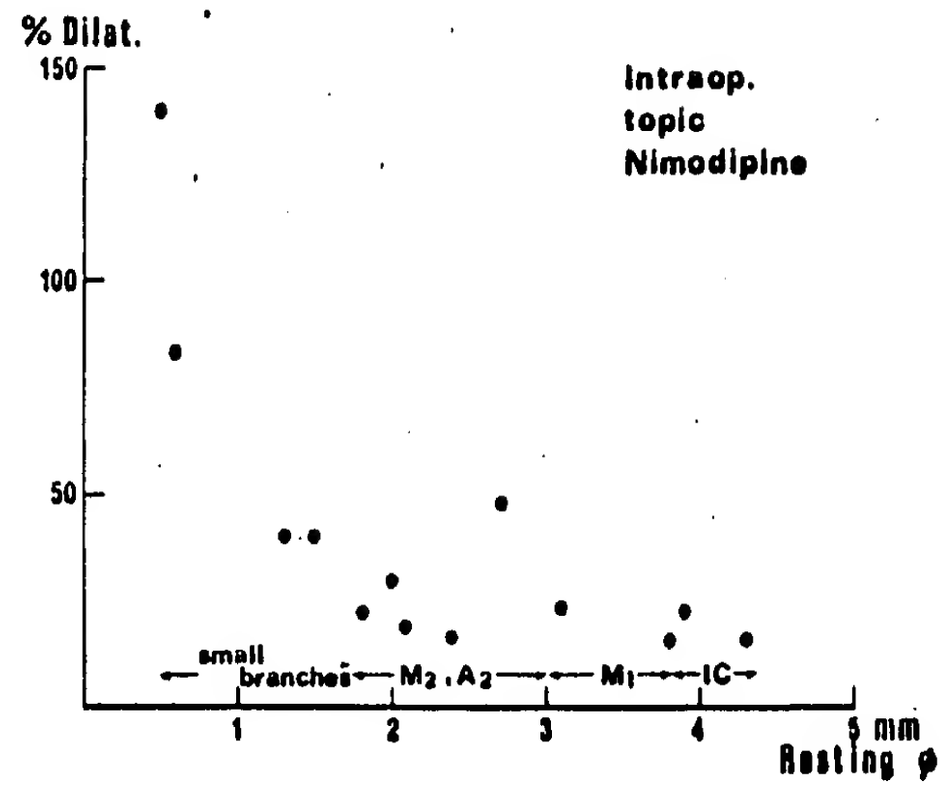

Fig. 1. Resting diameters of internal carotid artery (*IC*), trunk of middle cerebral artery (M_1), major branches of middle cerebral artery (M_2), distal anterior cerebral artery (A_2) and smaller branches like Heubner's artery, posterior communicating artery and anterior choroidal artery, plotted against percentage dilatation during intraoperative topical administration of 2.4×10^{-5} M Nimodipine

Postoperatively, 12 of the 17 patients treated intraoperatively had an uneventful course; 15 patients were free from symptoms on discharge. Two patients developed an intermittent neurological deficit; the control angiograms showing absence of relevant vasospasm. A third patient developed a hemiparesis on day 8 postoperatively together with deterioration of consciousness. On angiography, only very minor narrowing of the left M_2 and A_2 was seen.

Three days later, angiography revealed severe spasm without further clinical deterioration. Intracisternal administration at this time failed to influence the vasospasm. No complications attributable to Nimodipine were observed. Two patients developed a postoperative

neurological deficit combined with angiographically demonstrated vasospasm, though of a moderate degree. In one case, moderate asymptomatic spasm was dilated with topical application of Nimodipine 3 days postoperatively 2 days later, however, the patient developed an intermittent hemiparesis for 2 days. Thereafter, on discharge, he was free of symptoms. The second case developed aphasia and a worsening hemiparesis on day 6 after surgery within 24 hours. Postoperative angiography revealed right ICA and MCA spasm, that was reversed by intracisternal infusion of Nimodipine. Symptoms improved within the following week and the patient went home free of symptoms. The results of the CT scan, however, showed an infarct in the temporal lobe. Minor postoperative asymptomatic spasm was observed in 8 patients and reversal of the spasm by intracisternal Nimodipine was achieved in 5 of these cases. Prophylactic administration of the preparation to 7 patients without angiographically verifiable spasm led to vasodilatation in 5 cases.

In summary, none of the 20 patients experienced an irreversible neurological deficit as a result of vasospasm. Reversible symptomatic spasm occurred in 2 patients (10%). Intracisternal Nimodipine introduced during operation dilated cerebral vessels in 100% of cases and postoperative intracisternal administration was effective in 70% of cases.

Discussion

The present pilot study gives the following information:

1. Topically applied Nimodipine in a concentration commonly used dilates cerebral vessels and reverses moderate vasospasm intraoperatively. Moreover, this seemed to decrease the probability of severe postoperative symptomatic vasospasm. During the time in which the study was done, (*i.e.*, between January and September 1981), 6 patients were operated but did not receive Nimodipine treatment. In 2 of these patients — preoperatively grade III and II (Hunt and Hess) respectively — severe symptomatic vasospasm occurred after surgery; the interval between SAH and operation being 1 and 2 days and the interval from SAH to symptomatic vasospasm 5 and 9 days respectively. Preoperative CT scans showed severe SAH in one and moderate SAH in the other case.

2. Postoperative intracisternal Nimodipine dilates normal and spastic vessels in about 70% of cases and seems to improve the patients prognosis if symptomatic spasm occurs. The morbidity from vasospasm of this series of patients, though small, is significantly lower in comparison to previously published data mentioned in the introduction, since there were no irreversible complications and 10% reversible complications. The results of intracisternally administered Nimodipine, therefore, indicate a protective effect of this drug against symptomatic vasospasm. This should be taken into account in future trials with a view to overcoming the crucial problem of vasospasm, possibly by combining more than one way of drug administration. Moreover, very rapid treatment in cases of symptomatic spasm within a week after surgery should be considered. Later on, the risk of infection by keeping a cisternal catheter may be too high.

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Authors' addresses: Univ.-Doz. Dr. L. M. Auer, Universitätsklinik für Neurochirurgie, Auenbruggerplatz 22, A-8036 Graz, Austria, Dr. Z. Ito, Dr. A. Suzuki, and Dr. H. Ohta, Department of Surgical Neurology, Research Institute for Brain and Blood Vessels, 6-10, Senshu-kubota-machi, Akita 010, Japan.

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